REMARKS

1. *Status of the Claims*

Claims 1-16, 19-32 and 39 are pending.

Claims 1-16, 19-32 and 38 stand rejected.

Claims 1, 2, 8, 16, and 19-21 are amended herein.

Claim 38 is canceled by this amendment.

Claim 39 is new.

Reconsideration is respectfully requested.

2. *Claim Objections*

The Examiner noted that previously entered claim 33 was not numbered in accordance with 37 CFR 1.126, and the Examiner re-numbered this claim as claim 38. The Applicants apologize for this error and thank the Examiner for making the appropriate correction.

3. *Rejections Under 35 USC 112, First Paragraph*

The Examiner rejected claims 1-16, 19-32 and 38 as failing to comply with the written description requirement in that the claims contained subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the Application was filed, had possession of the invention.

The Examiner in particular pointed out the subject matter added by Applicants' amendment of February 1, 2003, to the definitions (q) and (r) of R^3 in claims 1 and 38, the definition (n) of R^3 in claim 2, and the definition (f) of R^3 in claim 16. The Applicants have amended claims 1, 2 and 16 to remove the language noted by the Examiner that was added by Applicants' last Amendment. Claim 38 has been canceled. Accordingly, Applicants believe that claims 1-16 and 19-32 as presently amended meet the requirements of 35 USC §112 first paragraph.

4. *Rejections Under 35 USC §103*

The Examiner rejected claims 1-16, 19-32

The Examiner rejected claims 1-7, 12, 32 and 38 under 35 USC §103(a) as being unpatentable over Faraci et al., WO 94/13643 (US 5712303). The Examiner re-iterated previous bases for rejection, stating, *inter alia*, that the difference between the teachings of Faraci et al. and Applicants' invention was that of generic description of the products being administered for the intended use. Claim 38 has been canceled as noted above.

The Applicants respectfully traverse the rejection of claims 1-7, 12 and 32 over Faraci et al. In order to rely on a reference as a basis for rejection of an applicants' invention, the reference must either be in the field of Applicants' endeavor or, if, not, then be reasonably pertinent to the particular problem with which the invention was concerned. *In re Oetiker*, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992). A reference from a different field may be reasonably pertinent if it is one that logically would have commended itself to an inventor's attention in considering the problem solved by the invention. *Wang Laboratories Inc. v.Toshiba Corp.*, 26 USPQ2d 1767 (Fed. Cir. 1993).

Faraci et al. discloses corticotropin release factor (CRF) antagonists, which are well known to be usable for treatment of stress related anxiety, depression, and other CNS disorders. Applicants' invention is directed to compounds that inhibit p38 MAP kinase for treatment of autoimmune conditions such as rheumatoid arthritis, bone resorption diseases and osteoarthritis, respiratory diseases and inflammatory conditions (see, e.g., p. 35 lines 1-10 of Applicants' specification). Faraci et al., makes a generalized assertion about CRF antagonists being usable for treatment of inflammatory disorders, upon which the Examiner has apparently focused. At the same time, the Examiner is overlooking the autoimmune and respiratory aspects of the diseases treatable by p38 MAP kinase inhibitors. The physiological bases for inflammatory conditions are both numerous and complex. p38 MAP kinase plays an important role in the translational control of tumor necrosis factor (TNF) and Interleukin (IL)-1, and p38 MAP kinase

inhibitors are recognized as being usable for treatment of diseases mediated by TNF-1 and IL-1 (p. 1-2 of Applicants' specification). Whatever anti-inflammatory capabilities may be exhibited by CRF antagonists, the Applicants respectfully point out that CRF antagonists have never been shown to modulate TNF or IL-1, or to otherwise be effective in the treatment of p38 MAP kinase inhibitor-mediated diseases such as arthritis, osteoarthritis rheumatism or respiratory conditions. Skilled persons, when designing p38 MAP kinase inhibitors, thus do not look to teachings related to drugs for different, unrelated targets such as CRF.

A *prima facie* case of obviousness requires, *inter* alia, some suggestion or motivation in the prior art to modify a reference, and a reasonable expectation of success from making such a modification. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Ligands that behave as antagonists for CRF could not reasonably be expected to have affinity for an unrelated target such as a kinase inhibitor, and persons skilled in the art would not be motivated to modify the chemical structure of a CRF antagonist in order to discover p38 kinase inhibitors. Further, since a CRF antagonist would not reasonably be expected to inhibit p38 MAP kinase, there could be no reasonable expectation of success in obtaining p38 MAP kinase inhibitors from modifying the CRF antagonists of Faraci et al.

Even if a finding of *prima facie* obviousness was proper in the instant case, the Applicants would request withdrawal of the rejection under 35 USC §103(a) in view of the results disclosed by Applicants specification that are entirely unexpected from the teachings of Faraci et al. Example 27 of Applicants' specification discloses that the compounds of Applicants' invention are effective at inhibition of p38 MAP kinase. This sort of activity would be unexpected from compounds obtained by modification of CRF antagonists such as those taught by Faraci et al. Further, Examples 28 and 29 illustrate the *in vitro* and *in vivo* inhibition of TNF alpha production by the compounds of Applicants' invention. Compounds designed by modification of CRF antagonists such as those of Faraci et al. could not reasonably be expected to inhibit TNF-α production as is achieved by the compounds of Applicants' invention. Still further, Example 30 shows that Applicants' compounds are effective in an *in vivo* arthritis assay.

Once again, the modification of CRF antagonists such as those of Faraci et al. could not be expected to provide such activity.

Accordingly, the Applicants submit that the Examiner's rejection of claims 1-7, 12 and 32 under 35 USC §103 as unpatentable over Faraci is not proper, and Applicants respectfully requests that this rejection be withdrawn.

a. Amendments to Claim 16.

The Applicants note that, in the Office Action mailed on October 25, 2002 in the instant case, the Examiner indicated that claims 8-11, 13-16 and 19-31 were objected to as depending from a rejected base claim but would otherwise be allowable if re-presented in independent form. Claim 16 was previously amended to place it in independent form. The Applicants have further amended claim 16 in this paper to include subject matter that the Examiner has previously indicated as being allowable. In particular, claim 16 as amended recites that R^3 may be selected from:

(a) heteroalkylamino;

(b) optionally substituted heterocyclylalkyl;

(c) optionally substituted heterocyclylalkoxy;

(d) optionally substituted heterocyclylalkylamino;

(e) -Y-(alkylene)-R^9 where Y is a single bond, -O- or -NH- and R^9 is optionally substituted heteroaryl, -$CONR^{12}R^{13}$, SO_2R^{14}, -$SO_2NR^{15}R^{16}$ - $NHSO_2R^{17}$ or -$NHSO_2NR^{18}R^{19}$ where R^{12}, R^{13}, R^{14}, R^{15}, R^{16} R^{17}, R^{18} and R^{19} are independently of each other hydrogen, alkyl or heteroalkyl; or

(f) Z-alkylene-$NR^{30}R^{31}$ where Z is -O-, and R^{30} and R^{31} are independently of each other, hydrogen, alkyl or heteroalkyl~~, wherein said alkylene and alkyl groups are optionally substituted with one to two groups selected from OH and O(alkyl)~~; ~~and~~;

(g) **heteroaryl selected from pyridinyl, N- xidopyridinyl or pyridonyl; or**

(h) substituted phenyl selected from sulfamoylphenyl, methylsulfonylphenyl, carboxyphenyl or ethoxycarbonylphenyl; and

Elements in claim 16 wherein R^3 is (a) through (f) were originally present when the Examiner indicated claim 16 as being objected to, but allowable in independent form. Element (f) has been amended to remove language which the Examiner indicated as not conforming to the requirements of 35 USC 112, discussed above.

The limitation of R^3 being heteroaryl selected from pyridinyl, N-oxidopyridinyl or pyridonyl, is derived from previously objected to claim 8 which the Examiner indicated would also be allowable if presented in independent form.

The limitation of R^3 being substituted phenyl selected from sulfamoylphenyl, methylsulfonylphenyl, carboxyphenyl or ethoxycarbonylphenyl is obtained from claim 13, which the Examiner indicated would also be allowable if presented in independent form.

Since independent claim 16 as amended contains only subject matter that the Examiner has previously deemed allowable, the Applicants believe that claim 16 as amended is presently allowable. Claims 19-32 and 39 depend from claim 16 either directly or indirectly, and are believed to be allowable for the same reasons as base claim 16. Claim 22 has been amended to remove "heteroalkoxy", for which no antecedent basis is provided by claim 16.

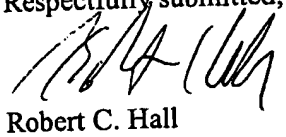
FEES

No fees should be due. Although four new claims are added, including an independent claim, in the last Office Action five claims were canceled, and the case contains less than three independent claims. However, in the event it is determined that a fee is due, please charge same to Deposit Account No. 18-1700.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-852-1141.

Respectfully submitted,



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